JUN 1 2004

Patent
Attorney's Docket No. 016800-438

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of	)	
	)	
De Lacharriere, Olivier et. al.	)	Group Art Unit: 1617
	)	
Application No.: 09/841,078	)	Examiner: Lauren Wells
	)	
Filed: April 25, 2001	)	Confirmation No.: 6852
	)	
For: Use of a Histamine Antagoinist, An Interleukin-1 Antagonist And/Or A TNF Alpha Antagonist In A Cosmetic, Pharmaceutical Or Dermatological Composition and Composition Obtained	)	

DECLARATION UNDER 37 C.F.R. §1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Jean-Claude Yadan hereby states as follows:

1) I was awarded a Doctorate in Bio-organic Chemistry from the University of Sciences (Paris VI) in Paris, France in 1983.

2) Currently I am CEO at Tetrahedron SAS, a new Medicinal Chemistry Company.

3) My curriculum vitae, research experience and list of publications are attached hereto as Appendix I.

4) I am aware that the Examiner in the above-identified application has concluded that claims 19-20 and 23-37 contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. I respectfully disagree with this conclusion.

5) I have reviewed the specification of the above-identified patent application. Based on 20 years of research in the Medicinal Chemistry field, it is my professional opinion that one of ordinary skill in the art, having read the specification, would have been enabled to make and/or use the invention defined in claims 19-20 and 23-37 without engaging in undue experimentation. That is, before the effective filing date of the above-identified patent application, those of ordinary skill in the art were familiar with IL-1 and TNF-alpha antagonists. In addition, the specification's disclosure of IL-

1 and TNF-alpha antagonists with varying chemical structures clearly conveys to those of ordinary skill in the art that any compound that exhibits IL-1 and/or TNF-alpha antagonist activity, regardless of its chemical structure, can be used in the claimed invention. It is evident that the application describes the compounds in a functional manner (i.e., in terms of the compounds' antagonist activity) because it is the compounds' functional characteristics, and not their chemical structures, which make the compounds suitable for use in the claimed compositions. In my opinion the terms "IL-1 antagonist" and "TNF-alpha antagonist" are the most appropriate terms to define the compounds employed in the claimed compositions. These compounds cannot be more precisely defined in the application without unduly restricting the scope of the pending claims. Therefore, it is my professional opinion that one of ordinary skill in the art having read the instant specification and being aware of the various well-known IL-1 and TNF-alpha antagonist compounds, would be able to practice the claimed invention without undue experimentation.

6. To support my opinion, I have conducted a search for technical references that show that IL-1 and TNF-alpha antagonist compounds were well-known and readily-identifiable before the above-identified patent application was filed.

First of all, concerning IL-1, it has been shown, in 1984, that cyclosporine therapy inhibits *in vivo* IL-1 release during the inductive phase (e.g. the 7-day treatment) (**1**). However, Bochner *et al.* describe the treatment of human lung fragments *in vitro* with dexamethasone or hydrocortisone resulting in dose dependent inhibition of IL-1 production (**2**). It has been confirmed in monocyte-like tumor cell line where 10nM of dexamethasone suppress totally IL-1 synthesis (**3**). In 1989, Gilbertsen et al. showed that CI-949, an antiallergy compound, is a weak inhibitor of IL-1 release from human peripheral blood lymphocytes (**4**). At the same time, it has been evidenced that hydroquinone inhibits macrophage production of IL-1 (**5**). Probucol, a NSAID, inhibits the IL-1 secretion from macrophages (**6**). Schnyder *et al.* experienced IX 207-887, a novel antiarthritic agent, showing that it is a good inhibitor of IL-1 release from monocytes (**7**). Plasminogen activator inhibitors may constitute a negative feedback pathway on monocytes-macrophage IL-1 release and subsequent immune activation *in vivo* (**8**). In 1991, Sawada et al. evidenced that FK506, an immunosuppressive agent, is effective as an inhibitor of non-Tcell response in vitro and affects not only IL-1 release but also IL-1 synthesis (**9**). Moreover, pentamidine, an aromatic diamidine used to treat pneumonia, induced inhibition of IL-1 via an alteration in the post-translational modificatio of the protein (**10**). Pyridazinones derivatives showed as good inhibitors of IL-1 release from mouse adherent macrophages (**11**). Naturally occurring IL-1 receptor antagonist has been shown to block IL-1 biological actions (**12**).

Concerning TNFα, incubation of human monocytes stimulated with LPS with misoprostol resulted in a reduction of IL-1 and TNFα production (**13**). Colchicine, a natural microtubule depolymerizing agent, caused a decrease in TNFα biosynthesis through the TNFα mRNA decreased production (**14**). Moreover, treatment of challenged mice with cyclosporin A led to an abrogation of IL-1 and TNFα releases (**15**). Erythromycin as well as roxithromycin inhibited TNFα release from human monocytes stimulated by LPS in a dose-dependent manner (**16**). Probhakar et al. have shown that

pentoxifylline, a methylxanthine derivative, selectively inhibited LPS-induced TNFα release. SF&F 86002, an inhibitor of 5-LO and CO in arachidonic metabolism, inhibited LPS-induced release of TNFα and IL-1 by two order magnitude more than pentoxifylline (17). Beta-glucan blocked the secretion of TNFα induced by bacterial LPS (18). Moreover, chloroquine reduced TNFα release from macrophage by disrupting TNFα gene transcription (19). Corticosteroids treatment of AIDS patients led to significantly less TNFα release from LPS-stimulated alveolar macrophages (20). Azelastine, a potent antiallergic agent, inhibited in a dose-dependent manner the TNFα production (21). Isoproterenol, a beta-agonist, rolipram, a PDE-IV inhibitor, and IBMX, a non-selective PDE inhibitor, significantly inhibited TNFα release in the LPS stimulated human whole blood (22). Theophylline suppressed the TNFα release by blood monocytes and alveolar macrophages as shown by Spatafora et al. (23). Quinine specifically blocked TNFα production of human alveolar macrophages at the level of gene transcription (24).

In summary, natural or synthetic low molecular-weight compounds as well as biological macromolecules were known to inhibit release or production or to antagonize the effects of IL-1 and/or of TNFα. All these data were available to those of ordinary skill in the art before december 1994.

7 The following references (1-24) show that IL-1 and TNF-alpha antagonist compounds similar to those disclosed in the instant specification were well-known before the application filing date. Copies of these references are attached hereto in Appendix II. In addition, the specification discloses tests, which are suitable for identifying compounds as IL-1 and TNF-alpha antagonists.

8. Based on my professional experience, and in view of the above-identified references, I believe that a person of ordinary skill in the art, having read the specification of the above-identified patent application, would have been readily able to identify compounds as IL-1 and TNF-alpha antagonist, and, thus, would have been enabled to make and/or use the invention defined in claims 19-20 and 23-37 without undue experimentation.

I HEREBY DECLARE that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date: May 19th 2004

Yasuo J.C. Jadza
(Name of Declarant)

APPENDIX I

(Curriculum Vitae, Research Experience and List of Publications)

Jean-Claude YADAN, PhD.
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14, rue des Meuniers
93100-Montreuil France

Background:

1983	PhD in Bio-organic Chemistry (Paris VI University)
1980	Master in Organic Chemistry (Paris VI University)

Professional Skills:

☐ ***as scientific researcher***

1979-1980	junior researcher at ENS/CNRS (***Prof. D. MANSUY***).
1981-1983	resaercher at CERCOA/*CNRS* (***Prof. F. LEGOFFIC***)
1984-1989	Head of chemistry laboratory/ Pharmaceutical Dept. of Research *Center Roussel-UCLAF* (Romainville, France).
1990-1991	Head of chemistry laboratory . in Research *Center* Bioxytech SA (Bonneuil/Marne, France).
1991-1995	Head of Chemistry Research Dept. Bioxytech SA / OXIS Int. SA (Bonneuil/Marne, France).
1995-1998	Scientific Director of Research *Center* OXIS Int. SA (Bonneuil/Marne, France).
1998-2000	Scientific and Technical Director Analytics Biophysics International SA (A.B.I.)
2001-	Scientific Director of Expertise and Consulting SARL

☐ ***as manager***

1989-1990	Funding of Bioxytech SA (Bonneuil/Marne, France) with 22 employees and 1500m²-area labs.
1990-1995	Manager of 8 researchers team
1996-1998	CEO, Directory Member,
1998-1999	Funding of Analytics Biophysics International SA
1999-2000	CEO, CA Member
2001-	CEO of Expertise and Consulting SARL
2003-	President of TETRAHEDRON SAS

- List of Scientific Publications -

Yadan, Jean Claude; Gonneau, Martine; Sarthou, Pierre; Le Goffic, François
« **Sensitivity to nikkomycin Z in Candida albicans: role of peptide permeases** »,
J. Bacteriol.; 160 (3), 884-888 (1984).

Gonneau, M.; Yadan, JC.; Sarthou, P.; Le Goffic, F.
« **Nikkomycin Z as inhibitor of Candida albicans growth** »,
In: Chitin Nat. Technol., [Proc. Int. Conf. Chitin Chitosan], 3rd Meeting; Muzzarelli, R. A.; Jeuniaux, C.; Gooday, G. W., Eds., Plenum, New York, pp. 203-205 (1985).

Nebot, C.; Moutet, M.; Huet, P.; Xu, J.; Yadan, JC. and Chaudière J.
« **Spectrophotometric Assay of Superoxide Dismutase Activity Based on the Activated Autoxydation of a Tetracyclic Catechol** »,
Anal. Biochem.; 214, 442-451 (1993).

Chaudière J, Moutet M, Monnier D, Duport JM, Lemainque A and Yadan JC
« **Measurement of alteration markers and protective systems** »,
Annales de Biologie Clinique; 51: 233 (1993).

Chaudière, J.; Yadan, JC.; Erdelmeier, I. and Moutet, M.;
« **Design of new selenium-containing mimics of glutathione peroxidase** »
In: Oxidative Processes and Antioxydants; Paoletti et al. Eds; Raven Press Ltd., New York; pp 165-184 (1994).

Chaudière, J.; Yadan, JC.; Erdelmeier, I.; Tailhan-Lomont, C. and Moutet, M.;
« **Nouveaux catalyseurs organoséléniés mimant l'activité de la glutathion peroxydase** »
C.R. Soc.Biol.; 188; 283-304 (1994)

Xu, J.; Yadan, J.C.
« **A new and convenient method for the synthesis of imidazole-2-thiones** »,
Synlett; 239 (1995).

Xu, J.; Yadan, J.C.
« **Synthesis of L-(+)-ergothioneine** »,
J.Org.Chem.; 60 (20), 6296-6301 (1995).

Xu, J.; Yadan, J.C.
« **First synthesis of (+)-Brazilane from (+)-Brazilin** »,
Tetrahedron Letters; 37 (14); 2421-2424 (1996)

Coutelle, C.; Lindenbaum, A.; Beeleville-Nabet, F.; Nicolas, MB.; Wellman, M.; Yadan, JC.; Leroy, P.
« **Méthodes de dosage du glutathion dans les milieux biologiques** »
Option/Bio; Supplément au n°170; 1-11 (1996)

Xu, J.; Yadan, J.C.
« **Synthesis of catechol derivatives: 5H-6, 6a, 7, 11b-tetrahydrobenzo[c]fluorene-3, 9, 10-triol** »,
submitted to Tetrahedron; (1997)

Yadan, JC.; Aguini, N.; Chaudière, J.;
« **Colorimetric Method of Measurement of Glutathione** »
in preparation, Method in Enzymology; (1997)

Chaudière, J.; Erdelmeier, I.; Moutet, M. and Yadan, JC.
« **One- versus two-electron transfers: Cytotoxic and cytoprotective effects of seleno-organic catalysts** »
submitted to Sulfur, Selenium and Telurium Chemistry; (1998)

Gerard-Monnier, D.; Erdelmeier, I.; Regnard, K.; Moze-Henry, N.; Yadan, JC. and Chaudière, J.
« **Reactivity of N-methyl-2-phenylindole with malondialdehyde and 4-hydroxy-alkenals- Part I: Application to a colorimetric assay of lipid peroxidation** »
submitted to Chemical Research in Toxicology; (1998)

Erdelmeier, I.; Gerard-Monnier, D.; Yadan, JC. and Chaudière, J.
« **Reactivity of N-Methyl-2-Phenylindole with malondialdehyde and 4-hydroxy-alkenals- Part II: Mechanistic aspects of the colorimetric assay of lipid peroxidation products**»
submitted to Chemical Research in Toxicology; (1998)

Erdelmeier, I. and Yadan, JC.
« **New method to introduce selenium atom in phenyl ring** »
in preparation (1998)

- List of Scientific Communications -

Chaudière J, Gérard-Monnier D, Moutet M et Yadan JC;
« **Méthodes analytiques: Quantification des systèmes de protection antioxydante et de la peroxydation des lipides** »,
Journée de formation I.S.P.B."Radicaux libres", Lyon, 1991.

Yadan, JC.; Aguini, N.; Chaudière, J.;
« **Specific and non-enzymatic determination of Glutathione in biological mixtures of Mercaptans** »,
Symposium on Free Radicals - Institut Pasteur - Paris - France, 1992.

Yadan, JC.; Aguini, N.; Chaudière, J.;
« **Fast and specific colorimetric assay of mercaptans with non-enzymatic discrimination of Glutathione** »,
in Free Radicals: From Basic Science to Medicine - Int. Soc. for Free Rad. Research - Turin, Italy; 1992.

Yadan, JC.; Antoine, M.; Aguini, N.; Tailhan, C.; Chaudière, J.;
« **Mercaptopyridine and Mercaptoquinoline from specific ß-elimination of Glutathione Thioethers** »
International Symposium on the Organic Chemistry of Sulfur (ISOCS 15) - Caen - France; 1992.

Yadan, JC.; Moutet, M.; Nebot, C.; and Chaudière, J.;
« **Superoxide Dismutase Activity: Measurement and Relationship with Glutathione** »
Microalgae and Health - 1st European Symposium - Montpellier - France; 1993.

Gerard-Monnier, D.; Erdelmeier, I.; Regnard, K.; Moze-Henry, N.; Yadan, JC. and Chaudière J.;
« **Fast and specific assay of enaldehydes by-products of lipid peroxidation based on the reactivity of substituted indoles** »
85th AOCS Annual Meeting; Atlanta, USA; May 1994.

Xu, J.and Yadan, J.C.;
« **New method for the preparation of 2-thio-imidazole: Total Synthesis of L-(+)-ergothioneine** »
16th International Symposium on the Organic Chemistry of Sulfur; Merseburg, July 1994.

Nebot, C.; Bonoron-Adele, S.; Tariosse, L.; Moutet, M.; Xu, J.; Yadan, JC. and Chaudière J.;
« **Scavengers of Ferryl Myoglobin protect the isolated heart from post-ischemic reperfusion injury** »
Lipoprotein Oxidation and Atherosclerosis; Pavia, Italy; September 1994.

Moutet, M.; D'Alessio, P.; Yadan, JC.; Erdelmeier, I. and Chaudière, J.;
« **GSH peroxidase mimics and endothelial cells** »
William Harvey Research Conferences, London, England; October 1994.

Chaudière, J.; Yadan, JC.; Erdelmeier, I.; Tailhan-Lomont, C. and Moutet, M.;
« **Design of new selenium-containing mimics of glutathione peroxidase** »
International Symposium on Nutrition and Antioxidants; Cannes, France; 1994.

Chaudière, J.; Moutet, M.; Yadan, JC. and Erdelmeiier, I.
« **Design of new glutathione peroxidase mimics for endothelial protection** »
2nd Winter Research Conferences; Les 2 Alpes; France; 1995

Gérard-Monnier, D.; Erdelmeier, I.; Moze-Henry, N.; Yadan, JC. and Chaudiere, J.
« **The reaction of N-methyl-2-phenylindole with the enaldehydes: Application to a novel assay of lipid peroxidation** »
21st ISF World Congress; The Hague; Netherlands; 1995

Erdelmeier, I.; Chaudiere, J. and Yadan, JC.
« **Copper(I) assisted mild and efficient synthesis of new Se-N-hetrocycles: Facile access to a promising class of Gpx mimics** »
11th IUPAC International Conference on Organic Synthesis; Amsterdam, The Netherlands, July 1996

Moutet, M.; Giroud, C.; Marshall, J.J.; Robinson, K.A.; Yadan, J.C. and Chaudiere, J.
« **Protective Effects of the Glutathione PeroxidaseMimic BXT-51072 in Models of Inflammatory Stress** »
VIII Biennial Meeting of International Society for Free Radical Research; Barcelona, Spain; October 1996

Yadan, J.C., Xu, J.; Appéré, G. and Aguini, N.
« **Seleno-organic pro-oxixdants as new anticancer drugs in hormone-dependent tumors** »
88th Annual Meeting of American Association for Cancer Research, San Diego, CA April 1997

Erdelmeier, I. and Yadan, JC.
« **Synthesis and Study of new seleno-organic mimics of glutathione peroxidase** »
213th American Chemical Society Meeting; San Fransisco, CA; April 1997

Ziemniak, J.A.; Moutet, M.; Yadan, J.C. and Mir N.
« **The Activity of a Novel Glutathione Peroxidase Mimic, BXT-51072, in Dextran sulfate-induced Inflammatory Bowel Disease** »
Annual Meeting of the American Gastroenterological Association and American Association for the Study of Liver Diseases; May 1997

Erdelmeier, I.; Taillhan-Lomont, C.; Moutet, M. ; Yadan, J.C.
« **Copper(I)-assisted Synthesis of new Se-N-Heterocycles and Study of their Activity as Mimics of Glutathione Peroxidase** »
VIIth International Conference on the Chemistry of Selenium and Tellurium; Vaalsbroek Castle-Aachen; July 1997

- Patents -

	Title	Inventors	Country	Filing N°	Filing Date	Patent N°	Pending Date
1	**Piègeurs de mercaptans, préparation**	Yadan et al.	France	9 114 782	91.11.29	9 114 782	11.02.94
2	**Procédé de dosage de l'activité SOD utilisant un composé autoxydable, nécessaire pour sa mise en oeuvre, composés autoxydables et leur préparation**	Xu, Jinzhu; Yadan, JC; Moutet, M; Chaudière, J.	France Germany UK Italy USA Japan	9 114 781 93 901 768.7 93 901 768.7 93 901 768.7 244 866 5-509 871	91.11.29 92.11.25 92.11.25 92.11.25 92.11.25 92.11.25	9114781 E692 12 334.2 E 0 625 209 E 0 625 209 5 543 298	23.12.94 17.07.96 17.07.96 17.07.96 06.08.96
3	**Composés autoxydables, préparation**	Xu et al.	France	9 202 082	92.02.24		
4	**Procédés spectrophotomètriques de dosage des mercaptans totaux, du glutathion réduit (GSH) et des mercaptans autres que le GSH dans un milieu aqueux, réactifs et nécessaires pour leur mise en oeuvre**	Yadan, JC; Antoine, M; Chaudière, J.	France Germany UK Italy USA Japan	9 115 868 93 902 331.3 93 902 331.3 93 902 331.3 695 705 5-511 476	91.12.20 92.12.15 92.12.15 92.12.15 92.12.15 92.12.15	9 115 868 E 643 698 E 643 698 E 643 698	23.06.95 05.03.97 05.03.97 05.03.97
5	**Procédé de dosage colorimètrique du dialdéhyde malonique et des autres énaldéhydes en tant qu'indices de peroxydation lipidique, nécessaires pour sa mse en oeuvre, indoles substitués utilisables dans ce procédé et leur préparation**	Gerard-Monnier D, Erdelmeier I, Chaudière J, Yadan JC.	France Europe USA USA Australia Canada Japan	9 305 430 94 916 258.0 362 418 702 197 67 955/94 2 139 591 6-525 048	93.05.06 94.05.06 94.05.06 94.05.06 94.05.06 94.05.06 94.05.06	9 305 430	28.07.95

6	**Nouveau Procédé de Préparation de l'ergothionéine**	Yadan, JC et XU, J.	France	9 315 457	93.12.22	9 315 457	13.10.95
			Europe	94 920 514.0	94.06.27		
			USA	194 457	94.02.08	5 438 151	01.08.95
			Australia	71 276/94	94.06.27		
			Canada	2 143 410	94.06.27		
			Japan	7-502 528	94.06.27		
7	**Utilisation de dérivés 2-mercapto-imidazole substitués en position 4 (ou 5) comme agents antioxydants, leur procédés de préparation et leurs applications en pharmacie, cosmétique ou alimentaire**	Yadan, JC; Xu, J; Moutet, M; Chaudière, J.	France	9 315 637	93.12.24	9 315 637	24.05.96
			Europe	95 904 589.9	94.12.22		
			USA	507 329	94.12.22		
			Australia	13 204/95	94.12.22		
			Canada	2 156 490	94.12.22		
			Japan	7-517 809	94.12.22		
8	**Nouveaux composés de structure benzisosélén-azoline et -azine, leur procédé de préparation et leurs applications thérapeutiques**	Erdelmeier, I; Chaudière, J; Moutet, M; Yadan, JC.	France	9 404 107	94.04.07	9 404 107	28.06.96
			Europe	95 916 723.0	95.04.07		
			USA		95.04.07		
			Canada	2 164 642	95.04.07		
			Australia	23 111/95	95.04.07		
			Japan	7-526 125	95.04.07		
9	**Utilisation de nouveaux composés séléniés comme agents pro-oxydants**	Xu, Yadan, Appéré et Chaudière J.	France	9 608 929	96.07.17		
			USA				
10	**Composés organoséléniés cycliques**	Erdelmeier et al.	France	9 616 102	96.12.27		
11	**Disélénures et sélénosulfures aromatiques**	Tailhan-Lomont et al.	France	9 616 103	96.12.27		

APPENDIX II

(Technical References)

1. Cyclosporine therapy of rat heart allograft recipients and release of interleukins (IL 1, IL 2, IL 3): a role for IL 3 in graft tolerance?
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Gilbertsen RB, Cullinen KM, Wilburn DJ, Dong MK, Conroy MC.

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7. Inhibition of interleukin-1 release by IX 207-887.
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Schnyder J, Bollinger P, Payne T.

8. Monocyte-macrophage release of IL-1 is inhibited by type-1 plasminogen activator inhibitors.
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9. Effects of an immunosuppressant, FK506, on interleukin 1 alpha production by human macrophages and a macrophage-like cell line, U937.
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10. Pentamidine: an inhibitor of interleukin-1 that acts via a post-translational event.
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